## Role of TrkB and B-catenin in plasticity and function of the visual cortex

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2014

# Summary

Over decades, the primary visual cortex (V1) has attracted the attention of neuroscientists as an ideal model system for studying sensory perception. Despite this attention, the question how the intricate pattern of neuronal connections necessary for the processing of visual information is formed has not been fully answered. While molecular cues and spontaneous neuronal activity determine the establishment of neuronal connections to a certain extent, visual experience plays an important role in refining these connections and their functional properties. An extreme example of the influence of visual experience can be observed in the binocular part of V1. This part contains neurons responsive to visual input to both eyes, with the contralateral eye (the eye on the opposite side of the head) being the dominant one. However, altered visual experience can strongly affect this ocular dominance and other functional properties like acuity (the spatial resolution of the visual system). For example eyelid closure in a four week old mouse, for a period of only three days, leads to a dramatically decreased responsiveness to the closed eye and a lower acuity of vision in that closed eye.

In this thesis we have studied experience-dependent plasticity in the mouse primary visual cortex. For this we have focused on TrkB signaling and on the protein β-catenin, and studied their role as potential molecular players in visual plasticity and function. TrkB is the receptor for BDNF, the most important neuronal growth factor in the brain which plays a crucial role in the formation and maintenance of synaptic contacts. β-Catenin is a protein which plays a role in the functioning of cell adhesion proteins involved in the formation of synapses, as well as in gene regulation. To study these proteins we have used transgenic strategies. Down regulation or full knockout of these proteins during early development is known to have profound effects on how the brain establishes its neuronal connections. Therefore, to circumvent these developmental issues ablation of β-catenin and down-regulation of TrkB signaling were both started after 5-6 weeks of age, so that neuronal circuits could be formed normally.

In chapter 2, the role of TrkB signaling in synapse maintenance was studied by expressing the protein TrkB.T1-EGFP in individual (sparse) excitatory neurons in the neocortex and hippocampus. This protein is a dominant negative version of TrkB, thereby interfering with endogenous TrkB signaling. Because the dominant negative protein was coupled to green fluorescent protein (EGFP) this allowed us to study morphological changes in TrkB.T1 expressing neurons within an unaffected environment. We focused on dendritic spines, protrusions from dendrites that form the post-synaptic sites of excitatory synapses. By imaging dendritic spines, we noticed that mature spines underwent a considerable decline after just a few weeks of TrkB.T1 expression in the cortex. In line with this, we observed a decreased amplitude and frequency of miniature post-synaptic currents that were recorded from TrkB.T1-EGFP expressing neurons in V1. Surprisingly, TrkB signaling did not seem to be crucial for maintaining spine stability in hippocampus, showing a brain region dependent role for TrkB.

In chapter 3 we further studied the effect of reduced TrkB signaling by expressing TrkB.T1-EGFP in most pyramidal neurons of the neocortex (opposed to the sparse expression used in chapter 2). Surprisingly, while expression in a sparse population of neurons led to a significant loss of mature synapses and reduction of synaptic currents, expression of the same transgene in the majority of pyramidal neurons in the cortex did not cause any changes in dendritic spines or in miniature post-synaptic currents. However, broad expression of TrkB.T1-EGFP led to a decrease in the efficacy of excitatory synapses, as well as a significant reduction of inhibitory innervations of excitatory neurons. Together, these findings show that broad expression of TrkB.T1-EGFP has profoundly different effects when compared to sparse expression, pointing towards a complex combination of possibly synaptic competition and homeostatic regulation governing the effects of TrkB.T1-EGFP expression.

In chapter 4 we studied the importance of TrkB/BDNF signaling during adulthood, when the network was already established, in regulating visual acuity in V1. We found that down-regulation of TrkB signaling in pyramidal cells in the mature visual cortex reduced synaptic strength and resulted in a loss of neuronal responses to high spatial-frequency stimuli. In spite of a significant loss of responsiveness in layer II/III pyramidal neurons of TrkB.T1-EGFP mice the response to strong stimuli, namely low spatial frequency, was not decreased. This change in visual acuity might be explained by a decrease in signal to noise ratio, an increase in size of the receptive fields of neurons or a decrease in perception of contrast. Single unit recordings indicated that signal to noise ratios and receptive field sizes were not changed after interfering with TrkB signaling. However, we found that V1 neurons in these mice were much less sensitive to contrast. To evoke the same response size, neurons in these mice had to be stimulated with much higher contrast visual stimuli compared to normal mice. We conclude that reduced perception of contrast is the underlying mechanism for reduced activity in TrkB.T1-EGFP mice. Our results also indicate that normalization has a cortical component and is not merely limited to earlier stages of visual processing.

Finally, in chapter 5 we focus on the role of another protein, β-catenin. This protein plays a role in both transcription and cell adhesion, and is essential for maintaining the synaptic machinery. Earlier studies indicated that β-catenin could potentially affect the acuity and plasticity of the visual cortex in adult mice. This is because β-catenin has been implicated in synaptic function and its activity-dependent plasticity via regulating cadherin-mediated cell adhesion and the synaptic recruitment of pre- and post-synaptic proteins. To test whether this was the case, we used a cre-lox system to ablate β-catenin in most pyramidal neurons of hippocampus and the neocortex after development. While ablation of β-catenin did not lead to a decrease in synaptic strength, or intrinsic firing properties, it did decrease NMDA receptor currents which seemed to be crucial for achieving normal visual acuity. Similar to the effect of

TrkB.T1 overexpression in V1, neuronal responses in β-catenin deficient mice were decreased only when high spatial frequency stimuli were shown but they were not affected when low spatial frequency stimuli were presented.

Interestingly, in spite of a different synaptic deficit in the two mouse lines studied in this thesis, the visual consequence of this deficit was very similar: reduced visual acuity through an attenuated perception of apparent contrast without changes in signal to noise ratios and receptive field sizes. Therefore, the work in this thesis shows that maintenance of synaptic function into adulthood is crucial for maintaining high acuity vision.